

Amendments to the Claims

Please replace the claim set on file with the Listing of the Claims presented below:

Listing of the Claims

Claims 1-200 canceled.

201. (Currently amended) A functional synthetic siRNA of 18-30 base pairs configured for interacting with a target mRNA of a target gene and silencing the target gene, the siRNA comprising:

(A) a sense strand comprising:

a first nucleotide of the sense strand closest to the 5' end of the sense strand having a 2'-O-alkyl modification; and

a second nucleotide of the sense strand next closest to the 5' end of the sense strand having a 2'-O-alkyl modification, wherein all nucleotides in the sense strand other than the first and second nucleotides have a 2'-OH and wherein the sense strand is devoid of a phosphate group at its 5' end; and

(B) an antisense strand which is at least substantially complementary with the mRNA of the target gene and the sense strand, wherein said antisense strand comprises:

a first nucleotide of the antisense strand closest to the 5' end of the antisense strand having a 2'-O-alkyl modification;

a second nucleotide of the antisense strand next closest to the 5' end of the antisense strand having a 2'-O-alkyl modification; and

a phosphate group at the 5' end of the antisense strand;

wherein all nucleotides in the antisense strand other than the first and second nucleotides have a 2'-OH; wherein the siRNA exhibits a reduction in the level of off-target gene silencing by both strands.

Claims 202 to 212 canceled.

213. (Previously amended) The siRNA of claim 201, wherein the antisense strand has at least one phosphorothioate internucleotide linkage.

Claims 214 to 219 canceled.

220. (Previously amended) The siRNA of claim 201, further comprising a 3' overhang of 1-5 nucleotides on at least one of the sense or antisense strand.

221. (Previously presented) The siRNA of claim 220, wherein the 3' overhang has at least one phosphorothioate internucleotide linkage or at least one methylphosphonate internucleotide linkage.

Claims 222 to 223 canceled.

224. (Previously amended) The siRNA of claim 201, further comprising at least one conjugate molecule coupled to the sense or antisense strand.

225. (Previously amended) The siRNA of claim 224, wherein the conjugate molecule is cholesterol.

226. (Previously amended) The siRNA of claim 225, wherein the conjugate molecule is coupled to the 3' end of the sense strand.

Claims 227 to 236 canceled.

237. (Previously presented) The siRNA of claim 201 wherein at least one of said 2'-O-alkyl modifications is a 2'-O-methyl modification.

238. (Previously presented) The siRNA of claim 201 wherein each said 2'-O-alkyl modification is a 2'-O-methyl modification.